Teratogens as therapy against cancer

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1. Introduction

Teratogens are defined as different types agents (chemical, physical, radiation, mechanical, infectious agents) that can produce morphological alterations in developing embryos.

Fig. 1: Example of how teratogens can affect development. In the picture, stuffed bicephalous calf at the Darlowo Muzeum, Poland.

A clear example of teratogen is thalidomide, which administration to pregnant women in the early 60s to fade typical nausea and vomiting, resulted in thousands of new-borns affected with phocomelia (absence of limbs). Thalidomide is used nowadays to treat multiple myeloma, inhibiting the Wnt signalling pathway.

2. Relation cancer-teratogens-development

There is a relation between cancer cells and developing embryos cells. If we think about them as two different tissues, both of them have similar characteristics, and teratogens strategy is used because of these similarities:

- They present a high proliferative ratio.
- Both of them activate some signalling pathways that are inactivated in most of normal tissues.
- They can change their phenotype and carry out similar movements, like methastasis in cancer or ingression during gastrulation in embryos.

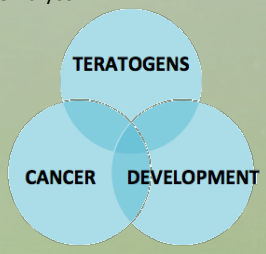


Fig. 2: Schematic representation of the relation between teratogens, cancer and embryonic cells.

3. Teratogens

3.1 Cyclopamine

Cyclopamine is a teratogen that causes cyclopia in sheeps and its mechanism of action is well known. It consists to inhibit the Sonic Hedgehog signalling pathway (Hh) by direct interaction and inhibition of Smoothened protein, leading to an inhibition of the pathway. This pathway is overexpressed in tumor cells, but also in embryonic tissues. Cyclopamine is used in chemotherapy to treat meduloblastoma.

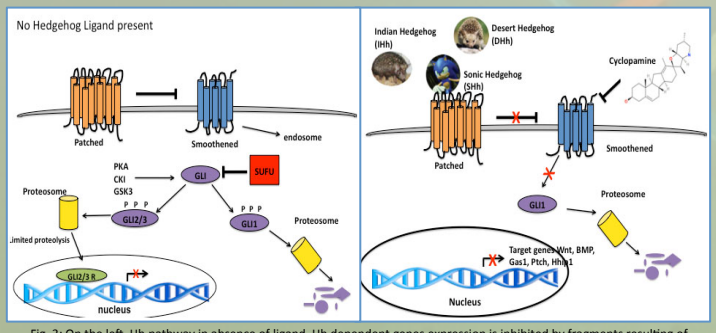


Fig. 3: On the left, Hh pathway in absence of ligand. Hh dependent genes expression is inhibited by fragments resulting of the Gli proteins limited proteolysis. If Smoothened is not inhibited, Gli won't repress gene expression. On the right, the effect of cyclopamine inhibiting Smoothened results in repression of expression. [3]

3.2 Valproic acid

Valproic acid is used to treat epilepsy and bipolar disorders. It inhibits histone deacetylase HDAC, a negative regulator of gene expression of the Wnt signalling pathway, which is very important in many processes, like proliferation, growth or survival, and mainly activated in embryonic tissues. In cancer cells is also reactivated, and this factor is very important in tumor initiation, metastasis and most of the hallmarks of cancer. Valproic acid is also used in combination with retinoic acid to treat breast cancer and inhibit tumor cell proliferation.

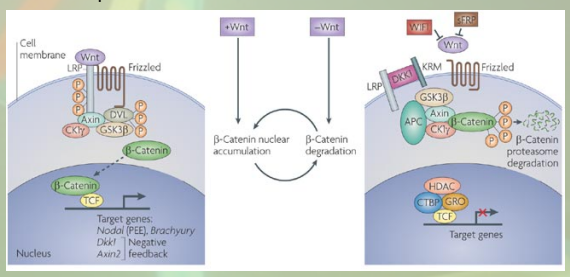
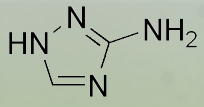


Fig. 4: Wnt-dependent signalling pathway in both ligand presence and absence situations. Thalidomide and Valproic acid inhibit the pathway with two different mechanisms. [4]

3.3 Retinoic acid

Retinoic acid has a totally different mechanism of action. It is a morphogen that helps defining the anteroposterior axis and its effects are mediated by the ligand-dependent transcription factors RAR and RXR. They regulate cell proliferation via dose-dependent modulation of the MAPK pathway: low concentrations of retinoic acid increases EGF signalling, stimulating cell proliferation, but higher doses inhibit cell division by decreasing ERK1 activation. Excess of retinoic acid in pregnant woman produces underdevelopment of kidneys in embryos.

4. New candidate for research: Aminotriazole.



- Used in farms to inhibit vegetal growth.
- It is mainly stored in young tissues and tissues with high proliferative activity.
- Causes teratogenia in chicken eggs, but not demonstrated in mammals.
- It is a competitive inhibitor of imidazoleglycerol-phosphate dehydratase, an enzyme that catalyses the seventh step of histidine production.

Tumor cells are in a high proliferative cell cycle status, and one of the most representative characteristics of aminotriazole is the fact that is mainly stored in these types of tissues. Aminotriazole could be a potential candidate to find new indications for it and be used in such important therapies as anti tumor.

[1] Blagosklonny MV. Teratogens as Anticancer Drugs. Cell Cycle 2005; 4:1518 - 1521; PMID: 16258270
[2] Developmental Biology. Seventh edition, 2003. Sinauer Associates.
[3] https://blogs.commons.georgetown.edu/au26/
[4] *Nature Reviews Molecular Cell Biology* **10**, 91-103 (February 2009)
[5] Fetal uptake and embryogenetic effects of aminotriazole in mice. Hans Tjälve. Archives of Toxicology. 25. IX. 1974, volumen 33, issue 1, pp 41-48.